Our patient, a 13-year-old girl, was found to have congenital afibrinogenemia in the neonatal period following bleeding from the umbilical cord stump. She was treated with repeated fibrinogen concentrate infusion. Coagulation studies at that time showed unmeasurable immunoreactive fibrinogen and bleeding time >30 min. Platelet count, platelet aggregation in response to adenosine diphosphate, and activity of FVIII/von Willebrand factor (vWF) were normal. Inheritance of the defect appeared to be autosomal recessive, as both parents were first cousins, had mildly reduced fibrinogen concentration and were asymptomatic [2]. Neither her three sisters nor two brothers were affected. She was referred to the gynecology clinic because of prolonged and excessive menstrual bleeding since menarche, 3 months previously, not responding to treatment with fibrinogen concentrate infusion (12 g over 3 months). Hemoglobin was 8.2 g/dl. Oral contraceptive (0.03 mg ethinylestradiol and 150 mg levonorgestrel) was prescribed without a break in pill taking, in order to inhibit subsequent menstruation. Bleeding stopped 2 days later without further menstrual periods over a 3-month follow-up. Hemoglobin is now 9.4 g/dl.

The use of oral contraceptive to inhibit ovulation in women with congenital afibrinoginemia was described by Bottini et al. [3] as a phrophylactic measure against hemoperitoneum caused by spontaneous rupture of corpus luteum. This complication is common, may recur, and does not always resolve with fibrinogen infusion, which leaves resection of ruptured ovarian tissue as only measure to control bleeding [1,3]. Besides the inherent risks of frequent use of blood products and of performing laparotomy in a patient with a bleeding disorder, removal of functioning ovarian tissues in young women has serious implications on future reproductive performance. We therefore agree that treatment with oral contraceptive is justified in women with congenital afibrinogenemia [1,3]. Although the first few ovarian cycles after menarche may be anovulatory without corpus luteum formation or risk of hemoperitoneum, as probably happened here, we recommend starting treatment as soon as possible after menarche because it is difficult to predict the onset of ovulation. Afibrinogenic women may sometimes have normal menstruation [4]. In such cases, oral contraceptive can be given for 21 days followed by a 7-day break, as usual, in order to inhibit ovulation and prevent hemoperitoneum. In patients with excessive menstrual bleeding, similar to our patient, the oral contraceptive should ideally be prescribed continuously without a break, in order to prevent menstruation as well as ovulation. Although oral contraceptive-withdrawal bleeding is usually of moderate amount, it is preferable not to expose those patients to any bleeding at all. The duration of contraceptive treatment in young women will depend on their reproductive wishes because these women can conceive [2]. Despite the finding that almost 90% of pregnancies reported were complicated by recurrent first trimester abortion, placental abruption and postpartum hemorrhage, successful outcome has been described in two women treated with fibrinogen replacement throughout pregnancy [5].

We therefore, believe, that oral contraceptive treatment is better given continuously to induce amenorrhea in women with congenital afibrinogenemia presenting with excessive menstrual blood loss.

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Hepatitis C Virus Infection in Waldenström's Macroglobulinemia

To the Editor: Recent reports suggest that some cases of Waldenström's macroglobulinemia (WM) are caused by hepatitis C virus (HCV) infection [1]. Previous studies from the Italian group suggested that HCV infection might also produce monoclonal gammopathies complicated by cryoglobulinemia (CG) [2]. We recently studied a case of WM following hepatocellular carcinoma in the course of chronic liver disease, suggesting that the persistent HCV infection and the history of alcohol abuse were involved in the pathogenesis of WM in this case (unpublished observation). Our preliminary report suggests the high incidence of HCV infection in B-cell malignancies in Japan [3].

We investigated four cases of WM since November 1992, when the assay system of HCV (enzyme immunoassay; EIA) was available at our institute. These four cases were all heterosexual Japanese. All the present cases of WM fulfilled the eligible criteria by Kyle and Garton [4]. Hepatitis B surface antigen (HBsAg) and antibody against HBsAg (HBsAb) were determined by EIA. Antibodies for HCV (HCVAb) were all examined by second generation EIA (Ortho Diagnostics Co., Raritan, New Jersey). We examined HCV-RNA in all the cases by reverse transcription-polymerase chain reaction (RT-PCR) assay, as described previously [5].

Table I shows the clinical characteristics of four cases. HCV-RNA was detected in only one of the four patients examined. The genotype of HCV was III (Okamoto's classification) in one case surveyed. CG was not present in any of the cases.

The incidence of HCV infection associated with WM is not well known. In our study, HCV infection was detected in only one of four WM patients examined. Santini et al. [1] reported that HCV-RNA was detected in all the examined cases. Nevertheless, three of our four WM cases were HCV-RNA negative. This finding is similar to the recent report by Mussini et al. [2]. However, RT-PCR was not done for the detection of HCV in this report. Although WM is usually diagnosed by an IgM value of >30 g/L, previous reports did not show the eligible criteria of WM. Therefore, secondary macroglobulinemia (<30 g/L of M component), such as type II mixed CG, might have been included in the previous studies. Since WM occurs in only 17% of patients with IgM monoclonal gammopathy [4], diagnosis based on the eligible criteria may be important.

A high incidence of B-cell malignancies is reported in HCV carriers associated with CG [2,6], suggesting that CG plays an important role in the pathogenesis of B-cell malignancies. In our patients, the onset of WM might be related to causes other than coexistence of CG, since CG was not documented. Type II mixed CG is endemic to the Mediterranean area, but, does not seem to be endemic in Japan. These findings suggest the heterogeneity in the pathogenesis of WM. Further studies are needed to clarify the involvement of HCV infection in the pathogenesis of WM.

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TABLE I. Characteristics of Patients With WM

Case No.	Age/Sex	IgM (g/L)	L chain	WM cells (%)	viscosity (cp)	ALT (mU/ml)	HCV-RNA	Genotype of HCV
1	34F	65.9	κ	17.0	5.16	78	Positive	III
2	44M	54.1	κ	63.2	4.77	11	Negative	(−)
3	73M	34.9	κ	57.0	n.d.	4	Negative	(−)
4	71M	56.8	λ	48.8	2.65	6	Negative	(−)

L chain, type of light chain, WM cells, atypical lymphoplasmacytoid cells in the bone marrow; viscosity, viscosity of the plasma (normal value = 1.72–2.03); ALT, alanine aminotransferase (normal value = 4–30); n.d., not determined.

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Fanconi Aplastic Anemia Associated With β-Thalassemia Trait

To the Editor: The coexistence of two genetic defects both associated with anemia may cause some clinical and hematological abnormalities, different from those found when they are present separately. In populations with a high incidence of β-thalassemia, such as Turkey, the combination of β-thalassemia mutation and another congenital hematological disorder may occur [1–2]. In Turkey, where the incidence of Fanconi's anemia (FA) also seems high, the coexistence of β-thalassemia trait and Fanconi's anemia in a patient was not surprising [3]. Examination of this child indicated changes in some of her hematological parameters during the severe anemia period, caused by FA and during the remission period which gave us some clues about the counter effects of both abnormalities on these hematological parameters.

Case Report

A 10-year-old girl (S.K.) was referred to our unit for evaluation of severe anemia. She was the third product of a consanguineous marriage, and one of her siblings had died previously of anemia and bleeding at age 8. Her past history revealed that she was diagnosed as having patent ductus arteriosis, which was corrected at the age of 15 months. Physical examination at this hospital at the age of 10 years revealed growth retardation and mild microcephaly. Her height was 127 cm, weight 23 kg (both measurements were less that the 3rd percentile for her age), and head circumference 50 cm. She had two café-au-lait spots, and her right thumb was dislocated. The results of laboratory examination of the patient and of her parents are shown in Table I. Karyotype analysis revealed 46 chromosomes with an XX pattern; an increased rate of spontaneous, and induced chromosomal breakage by diepoxy butane (DEB) was observed. The diagnosis of FA was made, and the patient was treated with oxymethalone 2 mg/kg and prednisolone 5 mg/day. The patient responded to this therapy well in 1 year (Table I). DNA analysis of the β-gene revealed heterozygosity for the IVS1-5 G-C mutation. During the 4-year of follow-up period, the patient remained well. Oxymethalon was tapered to 0.5 mg/kg. Some of the hematological values of the patient during the follow-up period are given in Table I.

The patient presented has FA and β-thalassemia trait associated with the IVSI-5 mutation. Absence of microcytosis during the severe anemia episode caused by FA indicated that the majority of the red blood cells produced by precursor cells are of a fetal line in which Hb synthesis was probably unimpaired because of the active synthesis of the γ-chain [4]. This observation supports the previous hypothesis that fetal red cell precursors are the most resistant cell lines of the marrow precursor cells to abnormalities causing bone marrow aplasia [5]. The presence of microcytosis in remission of FA indicated that the effect of thalassemia on red cell volume overcomes the effects of FA on the same parameter. This observation conflicted with the previous knowledge that in FA during remission or before the anemic episode macrocytosis would be present. This assumption may only be valid in FA patients without a coexistent thalassemic determinant.

This study indicates the importance of detailed hematological evaluation in FA, not only in the anemic period, but during remission as well. Such a detailed study will not only help detect the presence of another genetically transmitted hematological abnormality, but will also aid in understanding the countereffects of different genetic disorders when present in a patient.

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TABLE I. Some Laboratory Data of a Patient With Fancon's Anemia and B-Thal Trait and Her Parents

	Age/ Sex	Hb (g/dl)	WBC (mm^3)	MCV (Fl)	Plat.[a] (10^9/L)	Hb A_2[b] (%)	Hb F[c] (%)
Propositus	10F	4.2	3,000	113	20	—	16
	11	12.4	5,300	68	220	3.6	7
	14	11.0	6,000	68	+++	3.7	8
Father	40M	12.0	7,800	56–61	+++	4.0–4.7	0.5–0.6
Mother	38F	12.0	6,800	87	+++	2.6	0.6

[a]+++, sufficient amount with a good clumps.
[b]By microcolumn.
[c]By alkali denaturation.